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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/066,390
Filing Date: February 01, 2002
Appellant(s): PADGETT ET AL.

John E. Tarcza
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 18, 2006 appealing from the Office action mailed December 29, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,783,941	VIND et al	8-2004
WO 99/29902	ARNOLD	6-1999

Birkenkamp et al. "In vitro processing of heteroduplex loops and mismatches by Endonuclease VII" DNA Research, Vol. 2, (1995), pp. 9-14.

Oleykowski et al. "Mutation detection using a novel plant endonuclease" Nucleic Acids Research, Vol. 26, No. 20 (1998), pp. 4597-4602.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66-72, 78-83, 85 and 87-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The amendment to claims 66 and 67 of "defined composition containing enzymes wherein the enzymes consist essentially of" is apparently new matter. A careful review by the examiner of the specification failed to identify any support for this new limitation. The phrase never appears in the specification. This is

particularly evident since the phrase "defined composition" itself lacks any definition. In reviewing the specification, the examples demonstrate that a "defined composition" can be something other than a homogenously purified protein as shown at page 57 of the specification, where the CEL-I is simply drawn to fractions which have CEL-I activity (see page 57, lines 14-20). Example 9, which uses cloned CEL-I does not differentiate this issue because there is no indication that the enzyme was purified to a greater degree than in Example 1. As noted by the Federal Circuit in In re Wright, 9 USPQ2d 1649, 1650 (Fed. Cir. 1989) "We shall sustain this rejection. We agree with appellant that the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of §112. Nonetheless, the question remains as to whether the meaning of "not permanently fixed thereto" is sufficiently described in the specification to inform the public what said language is intended to encompass. From our review of the present disclosure, we are convinced that this limitation is subject to different interpretations and the specification is devoid of adequate guidelines to direct the public to the correct meaning."

The situation in Wright is precisely analogous to the current situation since the phrase "defined composition" is not sufficiently described to inform the public what compositions are "defined" and what compositions are not "defined". Apparently, Applicant would argue that a cell extract is "undefined" while a column fraction is "defined". In neither case is the composition limited to a homogenously

purified set of components, all of which could be identified, which is closer to what the ordinary practitioner would understand "defined" to mean.

Since no basis has been found to support the new claim limitation in the specification, the claim is rejected as incorporating new matter.

Claims 66-72, 78-83, 85 and 87-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "defined composition containing enzymes wherein the enzymes consist essentially of". In reviewing the specification, the examples demonstrate that a "defined composition" can be something other than a homogenously purified protein as shown at page 57 of the specification, where the CEL-I is simply drawn to fractions which have CEL-I activity (see page 57, lines 14-20). Example 9, which uses cloned CEL-I does not differentiate this issue because there is no indication that the enzyme was purified to a greater degree than in Example 1.

Therefore, is a defined composition something in which every element is precisely defined or is it simply something more purified than a cell extract or is a cell extract defined by the process of making. On the web, there are discussions of what "defined composition" is in the context of serum free media. For example "Serum-free medium on the other hand is a more defined medium. While composed of many constituents, the composition is known and the level of each component precisely

defined." See http://www.athenaes.com/WhySFM.htm. The specification does not teach or provide any situation where the entire composition is known and the leve of each component precisely defined, but rather teaches fractions from columns, which represent a different sort of composition than the "defined composition" in media.

Finally, using the broadest reasonable interpretation in concert with ordinary patent law, there is no question that a product by process claim "defines" the product, as noted in MPEP 2113, which notes that 'product-by-process claims are limited by and defined by the process." In the context of the Vind reference, the cell extract is defined by the process of making the cell extract and therefore, may reasonably be deemed a "defined composition" since the composition of the cell extract is defined by the process by which the cell extract is made, as per MPEP 2113 and In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985).

Claim Interpretation

Prior to analysis of the claims under the prior art, the scope and content of the claims must be analyzed. Here, it is the phrase "defined composition" and "consisting essentially of" which must be analyzed. For the reasons given above, the phrase "defined composition" is interpreted to encompass the cell extract of Vind. With regard to the attempt to limit the composition using the phrase "consisting essentially of", MPEP 2111 notes "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." Since the specification is entirely silent with regard to the phrase "defined composition" the phrase "consisting essentially of" is simply treated as

"comprising". This further supports the rejection since even if the cell extract were deemed not to be a "defined composition", the cell extract certainly comprises a "defined composition" of specific enzymes which function in the instantly claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 67, 69-73, 85 and 87-90 are rejected under 35 U.S.C. 102(e) as being anticipated by Vind (U.S. Patent 6,783,941) (who receives benefit of priority to 60/256,018, filed December 15, 2000).

Vind teaches an in vitro method of making linear sequence variants (see column 2, lines 47-67),from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs separated by complementary base pairs (see column 2, lines 47-67, column 4, lines 16-21 and column 7, lines 15-20, where only 70% identity between the strands is required which will inherently include many situations of non-complementary base pairs separated by complementary base pairs) comprising:

a) preparing at least one heteroduplex polynucleotide (see column 2, lines 47-67),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see column 17, example 2, where a cellular extract with the MutS mismatch repair enzymes are used, which extract will inherently comprise the naturally present exonucleases and polymerases such as Taq polymerase, which has exonuclease activity) and an agent with strand cleavage activity (see column 17, example 2, where the MutH enzyme, part of the MutS mismatch repair system, will also inherently be present and which has strand cleavage activity),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see column 2, lines 47-67, where the enzymes correct the heteroduplex).

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (see column 2, lines 47-67 and lines 45-46, which notes "new permutations of mismatches will be generated in the annealing step of each cycle" and see column 19, example 4, where resulting nucleic acids are recovered by cloning).

With regard to claim 69, Vind teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see column 17, example 2, where the cell extract is added).

With regard to claims 70-72, Vind teaches the addition of Taq DNA ligase (see column 17, example where the cell extract, which inherently includes the Taq ligase, is used).

With regard to claim 73, Vind teaches the MutS system enzymes which includes MutH that will have strand cleavage activity (see column 17, example 2).

With regard to claims 84-86, Vind teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see column 2, lines 61-63, where mismatch repair proteins repair mismatches to form homoduplexes).

With regard to claim 87, Vind teaches performance of the method to generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

With regard to claims 88-89, Vind teaches screening for changed properties of the sequence (see column 9, lines 6-12 and column 7, lines 28-38).

With regard to claim 90, Vind teaches 60% homology can be used which would result in three non-complementary base pairs (see column 7, line 43) and that performance of the method will generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941).

Vind teaches an in vitro method of making linear sequence variants (see column 2, lines 47-67) from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs separated by complementary base pairs (see column 2, lines 47-67, column 4, lines 16-21 and column 7, lines 15-20, where only 70% identity between the strands is required which will inherently include many situations of non-complementary base pairs separated by complementary base pairs) comprising:

a) preparing at least one heteroduplex polynucleotide (see column 2, lines 47-67),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see column 17, example 2, where a cellular extract with the MutS mismatch repair enzymes are used, which

extract will inherently comprise the naturally present exonucleases and polymerases such as Taq polymerase, which has exonuclease activity) and an agent with strand cleavage activity (see column 17, example 2, where the MutH enzyme, part of the MutS mismatch repair system, will also inherently be present and which has strand cleavage activity),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see column 2, lines 47-67, where the enzymes correct the heteroduplex)

d) separating and recovering at least one sequence variant having a sequence different from either polynucleotide strand in said heteroduplex (see column 2, lines 47-67 and lines 45-46, which notes "new permutations of mismatches will be generated in the annealing step of each cycle" and see column 19, example 4, where resulting nucleic acids are recovered by cloning).

With regard to claim 69, Vind teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see column 17, example 2, where the cell extract is added).

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With regard to claim 73, Vind teaches the MutS system enzymes which includes MutH that will have strand cleavage activity (see column 17, example 2).

With regard to claims 84-86, Vind teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see column 2, lines 61-63, where mismatch repair proteins repair mismatches to form homoduplexes).

With regard to claim 87, Vind teaches performance of the method to generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

With regard to claims 88-89, Vind teaches screening for changed properties of the sequence (see column 9, lines 6-12 and column 7, lines 28-38).

With regard to claim 90, Vind teaches 60% homology can be used which would result in three non-complementary base pairs (see column 7, line 43) and that performance of the method will generate a library of different nucleotide sequences (see column 9, lines 6-12, for example).

Vind does not teach adding the ingredients in the particular order claimed in claim 68.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any order of adding ingredients, as MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the first necessary reactant first, the second second and the third reactant needed is added last. So in the absence of any evidence of unexpected

results with regard to the order of addition, the claimed order is prima facie obvious as noted by the MPEP section above.

Claims 75-77 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941) in view of Arnold et al (WO 99/29902)

Vind teaches the limitations of claims 67, 69-73 and 84-90 as discussed above. Vind expressly suggests that any system which recognizes mismatches in duplex DNA sequences may be used (see column 5, lines 28-57), but Vind does not agents such as hydroxylamine or intercalating agents to induce heteroduplexes.

Arnold teaches the application of mismatch correction methods such as those of Vind to evolving polynucleotides by performing the steps in claim 66 to heteroduplex parental nucleic acids which are corrected to form a heterogenous population of homoduplex nucleic acids (see page 12, paragraph 3, for example). Arnold expressly teaches the use of in vitro DNA repair systems such as those of Vind (see page 17, line 30 to page 18, line 4).

With regard to claims 75-77, Arnold teaches mutagens such as chemicals like hydroxylamine (see page 10, line 30), intercalating agents (see page 10, line 33 to page 11, line 1) and ionizing radiation (see page 11, lines 1-3).

With regard to claim 80, Arnold teaches the use of E. coli extracts for repair, which will include E. coli Pol 1 (see page 17, line 33).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the mutagents of Arnold since Arnold expressly

teaches that the heteroduplex correction method may be performed in vitro and since Vind also teaches enzymatic correction of heteroduplexes to homoduplexes in vitro (see column 2, for example). It would further have been prima facie obvious to use the mutagens taught by Arnold since Arnold teaches that these are known equivalents. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941) in view of Birkenkamp et al (DNA Research (1995) 2:9-14).

Vind teaches the limitations of claims 67, 69-73 and 84-90 as discussed above. Vind does not teach the use of the T4 mismatch correction system.

Vind expressly teaches that a variety of different mismatch repair systems can be used (see column 5, lines 28-57).

Birkenkamp teaches an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), using the T4 mismatch correction

system, including T4 endonuclease VII, T4 DNA ligase and T4 DNA polymerase (see page 11, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the T4 mismatch correction system in the in vitro mismatch repair method of Vind since Vind notes "The instant invention however utilizes the very base pair mismatch correcting property of the mismatch repair system to generate diversity instead of limiting it (see column 5, lines 39-41)." Vind further notes that "The term "mismatch repair system" shall herein be understood according to the art as a system normally present within cells which recognizes mismatches in duplex DNA sequences (see column 5, lines 28-30)." So Vind is motivated to use ordinary mismatch repair systems in his diversity generation method and Birkenkamp teaches that the T4 system "In summary, these observations emphasize further the in vivo role of endonuclease VII as a repair-initiating enzyme that recognizes a wide variety of DNA secondary structures (see page 13, column 2)" Finally, since Birkenkamp teaches that the T4 system is a known equivalent in the prior art of the other systems detailed by Vind in column 5, this falls within the situation described in MPEP 2144.06, which notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to

render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Claims 66-74, 81-82, 85, 87-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vind (U.S. Patent 6,783,941) in view of Oleykowski et al (Nucleic Acids Research (1998) 26(20):4597-4602).

Vind teaches the limitations of claims 67-73 and 84-90 as discussed above. Vind does not teach the use of Cel I.

Oleykowski teaches that Cel I is a superior enzyme for mismatch correction (see page 4602, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Cel 1 of Oleykowski in the in vitro mismatch repair method of Vind since Oleykowski states,

"The principle of mismatch recognition by CEL 1 appears to be different from T4 endonuclease VII, which has also been used for enzyme mutation detection. The latter is a resolvase which nicks one stand at the site of a mismatch and then in the other strand across from the DNA nick. Therefore, any nick can produce two corresponding fragments of the two colors. In the case of CEL 1, the two fragments of the two colors represent two totally independent mutation detection events that complement each other to confirm the presence of the mutation. (See page 4602, column 1)."

Oleykowski further notes "Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-rnismatch DNA sequences.

Background non-specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

So, an ordinary practitioner would have two separate motivations to use CEL 1 in the method of Vind in the place of the other mismatch correction systems. First, CEL 1 operates differently than T4 endonuclease VII and only nicks one strand to result in truly independent mutation event detection. Second, CEL I mutation detection is simple, with low background nicking, high signal to noise ratio and uses a stable enzyme, which minimizes wasted effort in assays where the enzyme fails to function.

(10) Response to Argument

Introduction

The central issue in this case for the rejections under 35 U.S.C. 112, first and second paragraphs and 35 U.S.C. 102 is one of claim interpretation for the phrase "defined composition". The method of the invention was performed by Vind using the same enzyme activities, as discussed in the rejection. The Vind reference teaches the use of a particular composition from a particular source which will necessarily result in the presence of a particular set of components. Appellant argues that this composition of Vind is not a "defined composition". This argument attempts to maneuver through two contradictory issues. It is essentially contradictory to bring in a new, undefined term and state that there was possession but that this new term distinguishes the prior art

based upon the meaning of the term. Several of the 35 U.S.C. 103 rejections should apply under either interpretation of "defined composition" since the composition of Birkenkamp is purified enzymes and the composition of Oleykowski is a purified Cel I.

Issue 1 – Whether addition of the phrase "defined composition", which is entirely without basis in the specification, constitutes incorporation of prohibited new matter into the claims?

Legal Standard

A new matter rejection under 35 U.S.C. 112, first paragraph is based upon the requirement of that the "inventor had possession of the claimed subject matter at the time the application was filed." In re Alton, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). In the current case, Appellant admits at page 15 of the brief that the specification lacks express basis for the phrase "defined composition containing enzymes wherein the enzymes consist essentially of".

The Federal Circuit has identified three situations where support may be found even in the absence of express basis. The first is "obvious error". Here, Appellant makes no argument that this phrase represents an "obvious error" type correction of new matter and this does not appear to be the case. The second is where different language is used, and the Federal Circuit has indicated that ipsis verbis is not required. The Federal Circuit noted in In re Wright, 9 USPQ2d 1649, 1650 (Fed. Cir. 1989) "We shall sustain this rejection. We agree with appellant that the invention claimed does not have to be described in ipsis verbis in order to

satisfy the description requirement of §112. Nonetheless, the question remains as to whether the meaning of "not permanently fixed thereto" is sufficiently described in the specification to inform the public what said language is intended to encompass. From our review of the present disclosure, we are convinced that this limitation is subject to different interpretations and the specification is devoid of adequate guidelines to direct the public to the correct meaning." The third situation is where the language represents an inherent property. As the Federal Circuit noted in Kennecott Corp. v. Kyocera International Inc. 5 USPQ2d 1194, 1197 (Fed. Cir. 1987) "It was concluded that the express description of the inherent property, since not "new matter", could be added to the specification with effect as of the original filing date." However, it is also clearly not inherent that the enzymes must be in a "defined composition" as understood by Appellant since that would also require that the Vind reference anticipate the claims inherently. Therefore, Appellant is arguing the second situation, that of "ipsis verbis".

"The specification is devoid of adequate guidelines to direct the public to the correct meaning"

As the Federal Circuit noted in In re Wright, in sustaining the new matter rejection, possession requires that the public is informed of the scope of the claims. Here, Appellant argues that the enzymes used were highly purified, sometimes purchased from manufacturers, and points to specific enzyme activities such as those on page 11, last paragraph, page 21, first paragraph, etc. However, these pages of the specification never indicate that the enzymes were purified. At page 11, for example,

the enzymes are simply listed. No level of purity is required. In fact, at no place in the specification is a "defined composition" of enzymes discussed. With regard to the particulars of the Cel I enzyme actually used in the specification, the specification states "Aliquots of the CELI fractions having mismatch cleavage activity were stored frozen at -20°C. A series of five-fold dilutions of CELI fraction #5 were then analyzed for mismatch cleavage of radiolabeled mismatch substrate (see page 57, lines 14-18 of the specification)." This is the closest that this specification comes to a "defined composition" of CELI. This composition must contain the CELI enzyme, but is otherwise not defined in any way. Neither Appellant nor anyone else knows what is in fraction #5 other than Cel I. In fact, these fractions were likely less pure than those of Oleykowski, since Oleykowski used a further size exclusion chromatography step which the specification did not utilize. Therefore, Appellant is not in possession of the phrase "defined composition" because there is no "defined composition" taught directly or indirectly in the specification.

Separately, Appellant argues that the examiner understood the term "defined". This is an attempt to finagle, given the constraints placed on the examiner during the examination process. MPEP 707.07(g) expressly requries "On the other hand, a rejection on the grounds of res judicata, no prima facie showing for reissue, new matter, or inoperativeness (not involving perpetual motion) should be accompanied by rejection on all other available grounds." Thus, when the new matter is written, the PTO requires the examiner to attempt to interpret the claim for all other available grounds including prior art. Properly applying this requirement should not be construed as acquiescence

to the clarity of the claims or to whether there is possession of the claimed invention by Appellant.

Therefore, the current claims incorporate prohibited new matter since there is no showing that the Appellant had possession of the concept of a "defined composition" in this specification.

Issue 2 – Whether the phrase "defined composition", which is entirely without basis in the specification, is vague and indefinite under 35 U.S.C. 112, second paragraph?

Legal Standard

In In re Corkill, 226 USPQ 1005 (Fed. Cir. 1985), the Federal Circuit confronted an issue similar to the current fact pattern. The Court notes "The Board agreed with the examiner's position that it was not clear whether the particle sizes in the '615 claims referred to single zeolite crystals or to agglomerates comprised of smaller crystals." Id. at 1009. The court sustained the rejection since the claim was indefinite as to the composition. As MPEP 2173.02 notes "Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite."

The phrase "Defined Composition" is insolubly ambiguous

In the context of the current specification, the phrase "Defined composition" falls into that category of "insolubly ambiguous". There is no way to determine what elements are permitted in the composition. This renders the claim insolubly ambiguous because the ordinary practitioner is entirely unable to determine whether they are

infringing this claim element. While a homogenously pure enzyme might be deemed a "defined composition" without too much argument, the entire prior art rejection is focused on the question of whether a cell extract from a particular cell known to contain particular enzymes is a "defined composition" or not. Appellant argues here that absolute precision is not possible. That is not the issue. The issue is whether there is sufficient precision in this term to distinguish the cell extract of Vind from the fraction #5 of Example 1, from the initial column purification of Oleykowski from a homogenous enzyme. If the term is simply read broadly, all of these are "defined" to some extent or another and Vind properly anticipates the claims. However, Appellant argues that Vind does not teach a "defined composition", indicating that, at least to Appellant, the term has some limits. For example, where along the purification process is the composition finally "defined". Does definition occurr when the cell extract is formed from the celery (see page 56, lines 14-15 of the specification), when the extract is filtered through miracloth (see page 56, lines 15-18 of the specification), after ammonium sulfate precipitation of the extract (see page 56, lines 19-25) or after the Con A affinity column (see page 56, lines 28-30).

In fact, even the specification admits that there may be other, undefined elements in the composition, noting "In addition, the data demonstrates that it is CELI activity that is part of the GRAMMR method, rather than a coincidental effect resulting from the purifying steps used in extracting CELI from celery (see page 75, lines 13-17 of the specification)." The coincidental effect meant is that of addition elements in the Cel I extract.

Therefore, it is this undefined and unknown bound of what is a "defined composition " and what is not a "defined composition" which renders the claim indefinite.

Issue 3 – Whether the broadest reasonable interpretation in light of the specification of the phrases "defined composition" and "mismatch endonuclease" encompass the Vind extract and enzymes so that Vind is anticipatory?

Legal Standard

In making the determination that a claim is anticipated under 35 U.S.C. §102(b) two analytical steps are required. First, the claim language must be interpreted. Secondly, the construed claim must be compared to the prior art reference and the rejection must make factual findings that "each and every limitation is found either expressly or inherently in [that] single prior art reference." Celeritas Techs. Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1360 (Fed. Cir. 1998).

The Federal Circuit discussed claim interpretation by the PTO in In re Morris, where the Federal Circuit noted "[A]s an initial matter, the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." In re Morris, 44 USPQ2d 1023, 1029 (Fed. Cir. 1997). The decision of the court in In re Bigio, 72 USPQ2d 1209 (Fed. Cir. 2004) strongly supports the breadth of interpretation.

There the Court notes "[T]his court counsels the PTO to avoid the temptation to limit broad claim terms solely on the basis of specification passages." In concert with Morris and Bigio is the decision in In re American Academy of Science Tech Center, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004), where the Federal Circuit noted "We have cautioned against reading limitations into a claim from the preferred embodiment described in the specification, even if it is the only embodiment described, absent clear disclaimer in the specification."

Quite recently, the Federal Circuit remonstrated the USPTO, noting "paradoxically in this case, the PTO construed the claim narrowly, rather than broadly, by reading in the same limitation as did the district court. In doing so, the PTO erred for the same reasons as did the district court." SRAM Corp. v. AD-II Engineering, 05-1365, (Fed. Cir. 2006).

Claim Interpretation

Applying the broadest reasonable interpretation to the phrase "defined composition" where the term does not appear in the specification defined composition" supports the conclusion that the term is broadly interpreted to encompass the cell extract of Vind. There is no language of limitation which excludes the cell extract from being a "defined composition". With regard to the attempt to limit the composition using the phrase "consisting essentially of", MPEP 2111 notes "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." Since the specification is entirely silent with regard to the phrase "defined composition" the phrase

"consisting essentially of" is simply treated as "comprising". This further supports the rejection since even if the cell extract were deemed not to be a "defined composition", the cell extract certainly comprises a "defined composition" of specific enzymes which function in the instantly claimed methods.

With regard to the the phrase "mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatched nucleotides", the specification provides no specific definition of this term. However, the specification does recite a list of enzymes which may be used in the method as the strand cleavage activities at page 25. This list expressly includes endonuclease such as Dnase I which are significantly less specific than the Mut H enzyme of Vind. So the question is whether the phrase "at the mismatched nucleotides" requires a cleavage immediately adjacent to the nucleotide or a cleavage that may be somewhat downstream of the nucleotide. Since the specification lacks a definition and using the broadest reasonable interpretation, where an enzyme like DNAse I was included in the mix, the claim is broadly interpreted to permit cleavage that is not adjacent to the nucleotide. This interpretation is consistent with the specification, which expressly teaches several enzymes at page 25 which would not cleave immediately adjacent to the mismatched nucleotide, but which would cleave based upon the presence of the mismatched nucleotide and would cleave near the mismatched nucleotide.

Arguments

As discussed in the rejection, Vind teaches each and every limitation of claim 67 and the rejected dependent claims.

Appellant raises five specific arguments regarding the anticipation rejection. The first is that the Vind cell extract is not a "defined composition". As extensively discussed above, the undefined phrase "defined composition" is broadly interpreted as encompassing the Vind extract because there is no limitation within the phrase which excludes a cell extract. Even conceding that the extract has thousands of enzymes, these enzymes are all present in specific amounts which are capable of definition, if this is the only requirement that "defined composition" imposes. Since Appellant does not even know how "defined" the composition used in the specification is, it is impossible to distinguish the composition of Vind on this basis.

Appellant then argues that "consisting essentially of" should be read as limiting on the composition. This is in direct contradiction with USPTO policy as exemplified in MPEP 2111, which notes "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." Since the specification is entirely silent with regard to the phrase "defined composition" the phrase "consisting essentially of" is simply treated as "comprising". This further supports the rejection since even if the cell extract were deemed not to be a "defined composition", the cell extract certainly comprises a "defined composition" of specific enzymes which function in the instantly claimed methods.

Appellants third argument is that the Vind composition would not meet the requirement for a "mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatched nucleotides". Vind expressly teaches that the enzyme will

allow "the mismatch repair protein(s) to repair nucleotide mismatches in the heteroduplexes (see column 2, line 61)." This demonstrates that the enzymes of Vind are capable of cleaving sufficiently closely to the mismatch in order to permit repair of the mismatch, meeting the claim limitation as broadly required. In fact, since the enzyme mixture will cleave away the mismatch, the enzyme mixture of Vind necessarily cleaves immediately adjacent to the mismatched nucleotide when removing that nucleotide.

Appellant then comments that Vind uses bacterial enzymes while the Cel I is a plant enzyme. For claim 67, this is not relevant since the claim does not require the use of any particular species of enzyme whatsoever.

Appellant then argues that the order of steps is different from the Vind method. When Vind forms the heteroduplex by heating, Vind inherently must first form the heteroduplex in the solution before the enzymes, in the same solution, can interact with that heteroduplex. Thus, Vind inherently must perform the method steps in the same order as that claimed since Vind cannot contact the heteroduplex with the enzymes prior to formation of the heteroduplex. Further, even if the order of steps were different, the 103 rejection over Vind would apply, since alteration of the order of steps is prima facie obvious as per MPEP 2144, which notes "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results".

Appellant then argues that the enzymes used in Appellant's specification are different than the enzymes of Vind. This argument is not relevant since it does not

relate to the claims. The claims under the Vind 102 rejection do not incorporate any such limitations regarding the source of the enzymes.

Appellant then argues that Vind does not teach addition of a ligase subsequent to formation of the reaction mixture. There is no indication that claim 71 requires a particular time of addition of the ligase.

Appellant then argues that while Vind wishes to make a library, Vind did not exemplify such a situation. This argument is simply irrelevant. The issue is not what Vind actually exemplifies but whether Vind teaches formation of multiple different molecules. Vind expressly teaches this concept. In fact, this is the essential teaching and invention of Vind, to form a library, and Vind clearly anticipates claims 87 and 90.

Appellant then attempts to argue that when the claim says "enzyme or enzymes", it really means only "enzyme" and not the plural. The plain language of claim 67 permits the use of multiple enzymes, since the claim expressly states "enzymes wherein the enzymes consist essentially of an effective amount of an enzyme or enzymes with" the various activities. Appellants attempt to read the plural "enzymes" as singular does not change the language of the claim.

Appellant lastly argues some undefined improvements which lack evidentiary support and which represent attorney argument without evidentiary basis. These do not represent any sort of secondary considerations, which would not apply to the anticipation rejection in any case.

Issue 4 – Whether Vind renders the order of addition of the enzymes prima facie obvious?

Argument

Appellant argues that because Vind teaches the use of a cell extract, Vind cannot suggest alternate orders of addition of components because Vind is adding all of the components simultaneously. There is no question that Vind exemplifies only the cell extract situation. However, Vind clearly teaches the use of "purified" RCR extract (see column 19, line 21, for example). Vind further teaches the specific enzymes required for the assay (see column 8, lines 17-26, where 6 or 7 specific enzymes are mentioned). Therefore, the issue is whether one of ordinary skill in the art would have been motivated to use purified components and alter the order of addition these components. As noted in the rejection, MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction. Therefore, the only real issue is whether, when Vind teaches "purified" extract, one of ordinary skill would appreciate that the enzymes could be purified individually and added. The Federal Circuit has recently provided a detail explanation of the subsidiary requirement for motivation to combine in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006) noting,

> "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan

possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with several years experience, there is no doubt that the ordinary artisan possesses the knowledge and motivation sufficient to purify known enzymes using known purification schemes and add them in any order. Some of the listed motivations of Dystar, to result in a cleaner, more efficient and more durable assay, would motivate the ordinary practitioner to perform such a purification.

Issue 5 – Whether Vind in view of Arnold renders the substitution of E. Coli Pol 1 for the enzymes of Vind prima facie obvious?

Argument

Appellant argues that because E. Coli Pol 1 is not thermostable, the enzyme would not function in the method of Vind, and therefore, Vind teaches away from the use of this enzyme. The flaw in this argument is that Appellant is relying upon Vind's preferred embodiment and not the entire teaching of Vind. While Vind undoubtedly prefers thermostable enzymes (see column 8, lines 15-16), Vind expressly teaches a broader method which does not require the use of thermostable enzymes (see column 5, lines 50-56) where Vind lists enzymes which are not thermostable. While the Vind method prefers to perform multiple repeating steps of denaturation and recombination, Vind does not require repetition, as expressly indicated by the "optional" nature of the

repetition step at column 2, lines 65-68. Consequently, when Vind performs the method in a single step, the enzyme need not be thermostable since it will not need to survive multiple rounds of amplification. As MPEP 2124 notes "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971)." Here, where Vind has a broader disclosure teaching a single round of recombination, the fact that Vind prefers to perform the method in multiple rounds of denaturation and renaturation does not teach away from the single round embodiment. In the single round embodiment, substitution of the E. coli Pol 1 enzyme would be prima facie obvious, since Arnold teaches that these are known equivalents. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Further, in view of the recent Dystar decision quoted above, "If, however, as we have held as a matter of law, the level of skill is that of a dyeing process designer, then one can assume comfortably that such an artisan will draw ideas from chemistry and systems engineering—without being told to do so. Dystar at 1653. Therefore, given the very high level of skill in the art, as evidenced by the prior art where Dr. Vind is a Ph.D.

with years of experience working at Novozyme and Dr. Arnold is a Ph.D. with more than 20 years experience and a lab of more than 20 people, an ordinary practitioner reading the Vind reference would recognize, without being told to do so, that any functionally equivalent enzymes would be useful in the method of Vind since Vind expressly teaches this fact, stating "Independently of the precise molecular mechanism, the end result will be that the "mismatch repair system" normally limits the "diversity" within the cell, represented by those duplex DNA sequences that comprise mismatches. The instant invention however utilizes the very base pair mismatch-correcting property of the mismatch repair system to generate diversity instead of limiting it (see column 5, lines 39-42)." Vind then lists a non exhaustive series of enzymes which would function to perform mismatch repair. This, in combination with Arnolds teaching that E. coli pol 1 will perform heteroduplex repair in vitro, as discussed in the rejection, provides significant motivation to use the equivalent enzyme.

Issue 6 – Whether Vind in view of Birkenkamp renders the substitution of T4 enzymes for the enzymes of Vind prima facie obvious?

Argument

Appellant argues that because the T4 enzymes are not thermostable, the enzymes would not function in the method of Vind, and therefore, Vind teaches away from the use of this enzyme set. The flaw in this argument is that Appellant is relying upon Vind's preferred embodiment and not the entire teaching of Vind. While Vind undoubtedly prefers thermostable enzymes (see column 8, lines 15-16), Vind expressly

teaches a broader method which does not require the use of thermostable enzymes (see column 5, lines 50-56) where Vind lists enzymes which are not thermostable. While the Vind method prefers to perform multiple repeating steps of denaturation and recombination, Vind does not require repetition, as expressly indicated by the "optional" nature of the repetition step at column 2, lines 65-68. Consequently, when Vind performs the method in a single step, the enzyme need not be thermostable since it will not need to survive multiple rounds of amplification. As MPEP 2124 notes "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971)." Here, where Vind has a broader disclosure teaching a single round of recombination, the fact that Vind prefers to perform the method in multiple rounds of denaturation and renaturation does not teach away from the single round embodiment. In the single round embodiment, substitution of the T4 enzymes would be prima facie obvious, since Birkenkamp teaches that these are known equivalents. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Further, in view of the recent Dystar decision quoted above, "If, however, as we have held as a matter of law, the level of skill is that of a dyeing process designer, then one can assume comfortably that such an artisan will draw ideas from chemistry and systems engineering—without being told to do so. Dystar at 1653. Therefore, given the very high level of skill in the art, as evidenced by the prior art where Dr. Vind is a Ph.D. with years of experience working at Novozyme and Dr. Birkenkamp is a Ph.D. with at least 10 years experience, an ordinary practitioner reading the Vind reference would recognize, without being told to do so, that any functionally equivalent enzymes would be useful in the method of Vind since Vind expressly teaches this fact, stating "Independently of the precise molecular mechanism, the end result will be that the "mismatch repair system" normally limits the "diversity" within the cell, represented by those duplex DNA sequences that comprise mismatches. The instant invention however utilizes the very base pair mismatch-correcting property of the mismatch repair system to generate diversity instead of limiting it (see column 5, lines 39-42)." Vind then lists a non exhaustive series of enzymes which would function to perform mismatch repair. This, in combination with Birkenkamp's teaching that the T4 enzymes will perform heteroduplex repair in vitro, as discussed in the rejection, provides significant motivation to use the equivalent enzyme.

Issue 7 – Whether Vind in view of Oleykowski renders the substitution of Cel 1 for the enzymes of Vind prima facie obvious?

Legal Standard

The Federal Circuit has recently provided a detail explanation of the subsidiary requirement for motivation to combine in Dystar v. Patrick Co., noting,

> "Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references." DyStar v. Patrick Co., 80 USPQ 2d 1641, 1651(Fed. Cir. 2006).

The Dystar court clarifies that motivation exists when the improvement results in a more desirable process and the issue then devolves to whether the ordinary artisan possesses the knowledge capable of combining the references. Here, where the ordinary practitioner is a Ph.D. with several years experience, there is no doubt that the ordinary artisan possesses such knowledge. This experience is evidenced by the authors of the prior art references, many of whom are Ph.D. scientists with years of experience. The author of the primary reference is Dr. Vind, who is a Ph.D. with years of experience and Dr. Yeung (senior author on the Oleykowski paper) who is also a Ph.D. with years of experience.

Argument

Appellant argues that there is no motivation to substitute Cel 1 because Oleykowski does not teach the use of Cel 1 in DNA repair. In fact, Vind notes "The instant invention however utilizes the very base pair mismatch-correcting property of the mismatch repair system to generate diversity instead of limiting it (see column 5, lines 39-42). So Vind is most interested in mismatch correction from the mismatch repair systems. Oleykowski notes that "Cel 1 is most active on mismatch substrates (see page 4601, column 2)." Oleykowski further notes "In the presence of dNTP, a highly efficient mismatch correction system will have been reconstituted (see page 4602, column 1)." The ordinary practitioner, here a Ph.D. with years of experience, would be highly motivated to use the "highly efficient mismatch correction system" of Oleykowski in the method of Vind in order to permit Vind to "utilize the very base pair mismatch correcting property" to generate diversity.

Appellant then argues that the superiority of Cel 1 would not motivate the ordinary practitioner. However the specific advantages of Cel 1 are precisely the sort of advantages suggested by the Dystar court as motivation. Oleykowski teaches a number of motivations, noting "Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-rnismatch DNA sequences. Background non-specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

Consequently Vind, who is interested in a variety of homologous enzymes, and expressly indicates interest in mismatch correction enzymes, and has a Ph.D. with years of experience, is certainly capable of combining the Cel 1 enzyme of Oleykowski and would have been expressly motivated to do so in order to obtain the advantages of the Cel 1 enzyme, including simplicity, low background, and enzyme stability. These advantages are precisely the sort of motivations listed by the Federal Circuit in Dystar.

While Appellant argues that the combination is hindsight, given that the motivation test of the Federal Circuit is properly met by the teachings of Vind and Oleykowski, the combination is based on both explicit and implicit motivation, both types of motivation cited with approval by the Federal Circuit in Dystar.

The argument with regard to thermal stability has been addressed before, and since Vind permits the method to be performed a single time, thermal stability would not be an issue in a single round method as discussed above.

Finally, the argument regarding the use of enzymes from different species is directly addressed by Vind, who teaches enzymes from multiple different species (see column 5). This teaching expressly suggests that combinations of enzymes from multiple organisms can be used. In fact, when Vind uses the Taq ligase in the mixture of the Mut enzymes, Vind is using enzymes from two different organisms in a single reaction.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

JEFFREY FREDMAN
PRIMARY EXAMINER
11/29/06

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